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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/292,217 04/15/99 GILLIES

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S LEX-004

EXAMINER

ROBERT J  
ART UNIT

PAPER NUMBER

1644  
DATE MAILED:

03/20/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

**Office Action Summary**

Application No.

09/292,217

Applicant(s)

GILLIES, STEPHEN D.

Examiner

Jessica H. Roark

Art Unit

1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 22 December 2000.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-39 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1, 2 and 4-39 is/are rejected.
- 7) ☒ Claim(s) 3 is/are objected to.
- 8) ☐ Claims \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

- 15) ☐ Notice of References Cited (PTO-892)
- 16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_
- 18) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 19) ☐ Notice of Informal Patent Application (PTO-152)
- 20) ☐ Other:

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### RESPONSE TO APPLICANT'S AMENDMENT

1. The Art Unit location and the examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Jessica Roark, Art Unit 1644.

2. Applicant's amendment, filed 12/22/00 (Paper No. 9), is acknowledged.

Claims 1, 10, 12, 19, 20 and 25 have been amended.

Claims 28-39 have been added

*Claims 1-39 are pending and being acted upon presently.*

3. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.

This Office Action will be in response to applicant's arguments, filed 12/22/00 (Paper No. 9).

The rejections of record can be found in the previous Office Action (Paper No.8).

It is noted that New Grounds of Rejection are set forth herein.

4. The Non-statutory double patenting rejection is held in abeyance.

5. Upon consideration of Applicant's arguments, filed 12/22/00 (Paper No. 9); the previous rejection of claims 1-27 under 35 U.S.C. 112, first paragraph, has been withdrawn.

6. Claims 1-2, 4-27 and newly added claims 28-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gilles et al. (WO 92/08495), in view of O'Reilly et al. (Cell 88:277-285 1997).

Applicant's arguments, filed 12/22/00 (Paper No. 9), have been fully considered, but have not been found convincing essentially for the reasons of record set forth in Paper No. 8.

Applicant argues that O'Reilly's suggestion of a combined treatment for tumor therapy that targets both the tumor cell and endothelial populations only encompasses cytotoxic chemotherapy, not the cytotoxic immunoconjugate of the instant invention, for use in combined therapy with an antiangiogenic agent.

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Contrary to Applicant's assertions, it is clear in O'Reilly et al. from the text preceding the phrase "cytotoxic chemotherapy" that any agent that "selectively or specifically" targets the tumor cell population would be appropriate to combine with the angiogenesis inhibitor taught by O'Reilly et al. (page 282, 1<sup>st</sup> full paragraph, 2<sup>nd</sup> column). The immunoconjugate taught by Gilles et al., as well as the immunoconjugate of the instant disclosure, are each agents that "selectively and specifically" target tumor cells. Furthermore, it was well known in the art at the time the invention was made that the end result of "cytotoxic chemotherapy", i.e., tumor cell death, can also be accomplished via immunoconjugates that induce a cytotoxic response. In addition, the advantages offered by a therapeutic agent that produced a selective cytotoxic response were appreciated by the ordinary artisan, since it was also well known to the ordinary artisan at the time the invention was made that standard cytotoxic chemotherapy was highly unselective in the cell types killed. Thus it would have been obvious to the ordinary artisan at the time the invention was made to substitute the cytotoxic immunoconjugate taught by Gilles et al. in any therapy involving cellular cytotoxicity.

Applicant is reminded that specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involves not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art. See CTS Corp. v. Electro Materials Corp. of America 202 USPQ 22 (DC SNY ); and In re Burckel 201 USPQ 67 (CCPA).

Applicant further argues that the prior art of Gilles et al. and O'Reilly et al. do not provide a reasonable expectation of success because the action of a cytokine as an inducer of an immune response relies upon access of cells of the immune system via blood vessels, and that an angiogenesis inhibitor would therefore be expected to reduce or eliminate the immune response.

Applicant's argument that an angiogenesis inhibitor would interfere with facilitation of the immune response by the cytokine immunoconjugate is found unpersuasive. Angiogenesis refers to the formation of new blood vessels and would not reasonably be expected to interfere with established vasculature. Neither the prior art nor Applicant provides any indication that the ordinary artisan thought that an angiogenesis inhibitor would interfere with recruitment of leukocytes. In contrast, O'Reilly et al. clearly expected that combined therapy of an angiogenesis inhibitor with tumor cytotoxic agents would be better than single agent treatment. Since most, if not all, tumor cytotoxic agents are themselves administered via the blood, the ordinary artisan clearly did have a reasonable expectation of success in combining an immunoconjugate as taught by either Gilles et al. or the instant disclosure, and an angiogenesis inhibitor as taught by O'Reilly et al.

Newly added claims 28-30 limit the cytokine of the immunoconjugate to a "lymphokine". Lymphokines are also clearly encompassed in the immunoconjugate of Gilles et al. (e.g., bridging sentence of pages 8-9 and Examples 6-7); thus the lymphokine species of claims 28-30 is also unpatentable over the prior art of Gilles et al. in view of O'Reilly et al.

Newly added claims 31-39 recite a method of reducing tumor size. Reduction of tumor size would be an expected property of any tumor cytotoxic response; therefore newly added claims 31-39 are also unpatentable over the prior art of Gilles et al. in view of O'Reilly et al. for the reasons of record and as discussed supra.

Thus Applicant's arguments with respect to the instant claims are not found persuasive. The rejection is maintained

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7. Claims 1, 11, and 26 are rejected as being unpatentable over Gillies (WO 92/08495) in view of O'Reilly et al. 1994 (Cell 79:315-328 1994) or Brooks et al. (Cell 79:1157-1164 1994) or Ingber et al. (Nature 348:555-557 1990).

The rejection of claims 1, 11, and 26 addressed specific forms of angiogenesis inhibitors. Applicant's arguments with respect to Gillies have been addressed supra. Applicant again argues no motivation to combine the references on the grounds that none of O'Reilly et al. 1994, Brooks et al., or Ingber et al. teach combining an angiogenesis inhibitor with an immunoconjugate. However, as discussed supra and pointed out previously in Paper No. 8, the ordinary artisan clearly appreciated that therapies targeting both the tumor and endothelial population could be beneficially combined.

The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Sernaker, 217 USPQ 1, 5 - 6 (Fed. Cir. 1983).

Applicant's arguments are not found persuasive.  
The rejection is maintained.

8. Claim 3 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

9. No claim allowed

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

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11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Jessica Roark, Ph.D.  
Patent Examiner  
Technology Center 1600  
March 15, 2001

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PHILLIP GAMBEL, PH.D  
PRIMARY EXAMINER  
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3/19/01